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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	14

DATE MAILED: 12/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,212	TIKOO ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *3,4,7,8,18-20,23,24,29-34,36-40,44,45 and 52-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 6, 9-17, 21, 22, 25, 27, 28, 35, 41-43, 46-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3, 10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group I, with the additional election of fiber protein and antigenic epitopes in Paper No. 13 is acknowledged. The traversal is on the ground(s) that groups I-IV are related as a combination/subcombination and therefore the groups should be searched together. This is not found persuasive because the combination ABC (or ABCD) does not necessarily rely solely either subcombination for patentability as evidenced by both subcombination being within the combination. The bovine vector construct with altered tropism is made by replacing the capsid with a heterologous capsid sequence. The combination contains adenovirus sequences including E1 and E3 (ABC, group I), the subcombination of adenoviral E1 deletion construct contains all adenoviral sequences minus E1 (AC, group II) while the subcombination of adenoviral E3 deletion construct contains all adenoviral sequences minus E3 (AB). The addition of a heterologous sequence other than the heterologous capsid sequence contains adenovirus sequences including E1 and E3 (ABCD, group IV). The subcombination of adenoviral E1 deletion construct with a heterologous sequence contains all adenoviral sequences minus E1 (ACD, group II) while the subcombination of adenoviral E3 deletion construct with a heterologous sequence contains all adenoviral sequences minus E3 (ABD). Therefore, upon review of the restriction requirement it appears that claim 22 should not have been placed with Groups I , II and III but should have only been included with Group IV. In the interest of compact prosecution claim 22 will be examined with group I as applicants have elected an antigenic epitope for examination. A heterologous capsid in a viral vector construct will necessarily be an antigenic epitope as the capsid protein is accessible to detection by the immune system. The requirement is still deemed proper and is therefore made FINAL.

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper Nos. 3 and 10, is attached to the instant Office Action.

Drawings

The office acknowledges that applicants have attempted to correct the drawings. However, the drawings are objected to please see Notice of Draftsperson's Review attached to the instant Office Action. Correction is required.

Claim Rejections - 35 USC § 112

Claims 1, 2, 12, 13, 14, 21, 22, 25, 27, 28, 35, 43, 50, 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for changing the viral tropism of a bovine adenovirus to infect a human cell line by substituting the human adenovirus fiber protein, does not reasonably provide enablement for altering the viral tropism by changing only the hexon or penton protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*,

858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. Such an analysis does not need to be specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection.

The specification teaches the insertion of a heterologous fiber protein into the bovine adenovirus to alter the viral tropism. The prior art indicates that in order to achieve viral entry of a recombinant virus more than just the fiber protein may need to be mutated. Krasnykh et al. (Journal of Virology, 1996, see IDS, see page 6844, column 2, 3rs paragraph) following viral attachment via the fiber knob domain, the next step in adenovirus infection is internalization of the virus via receptor-mediated endocytosis. This process utilizes the penton base with secondary host cell receptors. These secondary receptors are responsible for the major aspects of internalization after fiber binding. Recombinant fiber binding its receptor does not trigger internalization. However, association of the recombinant fiber with recombinant penton base does trigger internalization. Reddy et al. (Journal of Virology, 1999, see IDS, see page 9143, last paragraph) indicates that more than the fiber protein is needed to introduce the bovine adenovirus construct into a human cell line. The RGD motif, which interacts with surface integrins and facilitates the entry of virus into cells, is present in the penton base protein of HAV-5 but absent in BAV-3. Introduction of such a motif into BAV-3 may facilitate entry into human cells. The specification does not teach altering the hexon or penton base only in order to facilitate entry of the virus into a human cell or non-bovine cell. However, there is no evidence or guidance in the

specification of creating mutation in only the viral penton and hexon protein that will facilitate infection in normally non-permissive cells. The enabling disclosure is clearly not commensurate in scope with these claims. Clearly there is lack of guidance directing a skilled artisan to practice the instantly claimed methods. Other than the specific viral mutations taught in the specification which contain a heterologous human adenoviral viral fiber protein that is able to infect a select group of human derived cell lines. Without specific guidance or direction and/or working examples, one of ordinary skill in the art would not be able to reproducibly practice the entire scope of the invention as claimed, without undue experimentation.

incomplete thought

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 6, 9-11, 14-17, 21, 22, 27, 28, 35, 41, 42, 43, 46-49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittal et al. (U.S. Pat. No. 5,820,868, 1998, see IDS Paper No. 3), Krasnykh et al. (Journal of Virology, 1996, see IDS Paper No. 3) and Reddy et al. (Journal of Virology, 1999, see IDS Paper No. 3).

The instant claims are drawn to a bovine adenovirus vector having altered tropism by the modification of a capsid protein (claims 1, 35) and a cell line expressing the recombinant adenovirus (claims 27 and 28). Specifically, the fiber protein is replaced with a heterologous fiber protein (claims 2, 5,6, 9, 10, 11, 15, 16, 17, 21, 22, 41, 42). The bovine adenovirus backbone construct is bovine subtype 3 (claims 12). An immunogenic composition comprising a bovine adenovirus with altered tropism in which the fiber protein has been replaced with a heterologous fiber protein (claims 43, 46-51)

Mittal et al. disclose the production of a recombinant bovine adenovirus for the production of foreign proteins, which are immunogenic and can function as a vaccine (see column 1,lines 28-33; column 13, lines 18-20; column 13, line 65 to column 14, line 10). The reference discloses a recombinant vector system comprising the entire BAV DNA and a plasmid or virus by *in vivo* recombination following cotransfection of a suitable cell line (column 4, lines 48-55). The reference also includes a method for providing a gene to a mammal in need thereof to control a gene deficiency which comprises administering to said mammal a live recombinant bovine adenovirus containing a foreign nucleotide sequence encoding a non-defective form of said gene under conditions wherein the recombinant virus vector genome is incorporated into said mammalian genome or is maintained independently and extrachromosomally to provide expression of the required gene in a target organ or tissue (column 5, lines 33-42). The reference

discloses the sequencing of the BAV E3 and fiber genes (see example 3). The general organization of adenovirus genomes seems to be well conserved; therefore, the regions of sequences could be predicted from the human adenovirus genome map. The fiber protein is present on the surface of the virion and is involved in a number of functions including attachment of the virus to the cell surface during infection, assembly of virion and antigenicity (column 23, lines 49-53). The BAV fiber gene encodes a protein of 976 residues if no splicing occurs, this is 394 amino larger than the Had2 fiber protein (column 23, lines 65-67). The reference also teaches inserting heterologous sequences in the E1 or E3 region of BAV (see examples2 and 4). The reference does not teach inserting a heterologous sequence into the fiber region or modifying the fiber region of a bovine adenovirus in order to alter the tropism of the virus.

Krasnykh et al. teach the modification and alteration of the adenoviral fiber protein in order to alter the viral tropism. The modification of the fiber protein alters the receptor recognition profile of the virus (see abstract). The reference discloses a rescue system to create an adenovirus containing modified fibers. Following viral attachment via the fiber knob domain, the next step in adenovirus infection is internalization of the virus via receptor-mediated endocytosis. This process utlizes the penton base with secondary host cell receptors. These secondary receptors are responsible for the major aspects of internalization after fiber binding. Recombinant fiber binding its receptor does not trigger internalization. However, association of the recombinant fiber with recombinant penton base does trigger internalization. On the basis of this recognition, strategies have been proposed to alter viral tropism by modulating the penton-

integrin component of the adenovirus entry pathway (see page 6844, column 2, 3rd paragraph). The reference does not teach modifying tropism of a bovine adenovirus.

Reddy et al. teach the production of a replication defective bovine adenovirus (BAV-3) and a method of reducing occurrence of replication competent adenovirus by the use of a cell line that complements those deleted proteins. The complementing cell lines expresses the necessary components from human adenovirus sequences further reducing the likelihood of producing replication competent viruses in the system (see page 9143, column 1, 3rd paragraph). The reference expressly directs using BAV-3 as a viral vector for therapy in humans. For successful therapy, transfer vectors with very high transudation efficiency are needed. A strategy to achieve this is to replace the knob region of the fiber of BAV-3 with that of an HAV. This is possible, as the entry of ovine adenovirus into human cells was enhanced when the knob region of the fiber was replaced with that of HAV-5. The RGD motif, which interacts with surface integrins and facilitates the entry of virus into cells, is present in the penton base protein of HAV-5 but absent in BAV-3. Introduction of such a motif into BAV-3 may facilitate entry into human cells (see page 9143, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a bovine adenovirus for the transuduction of human cell lines or for the use of the bovine adenovirus as a vaccine vector. Reddy et al. teaches producing a bovine adenovirus with altered tropism to infect human cells. Krasnykh et al. teaches that the adenoviral vector can be directed to different cell types by altering the fiber protein of the adenovirus. While Mittal et al. teach utilizing bovine adenovirus for the production of foreign genes in a cell and for utilizing the virus as a vaccine vector. One having ordinary skill in the art would have

been motivated to utilize the bovine adenovirus as a vaccine vector because the average human population would not have produced neutralizing antibodies to bovine adenovirus as this virus would not normally infect the population. Utilizing a bovine adenovirus as a vaccine vector would also reduce the risk of recombination with wild type viral sequences creating a replication competent virus. Therefore, the instant invention is obvious over Mittal et al., Krasnykh et al. and Reddy et al.

Claims 1, 2, 5, 6, 9-17, 21, 22, 27, 28, 35, 41, 42, 43, 46-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Romanczuk et al. (WO 99/36545, see IDS Paper No. 3) and Reddy et al. (Journal of Virology, 1999, see IDS Paper No. 3).

The instant claims are drawn to a bovine adenovirus vector having altered tropism by the modification of a capsid protein (claims 1, 35) and a cell line expressing the recombinant adenovirus (claims 27 and 28). Specifically, the fiber protein is replaced with a heterologous fiber protein (claims 2, 5,6, 9, 10, 11, 15, 16, 17, 21, 22, 41, 42). The bovine adenovirus backbone construct can be bovine subtuype-1, 2,or 3 (claims 12, 13, 14, 50). An immunogenic composition comprising a bovine adenovirus with altered tropism in which the fiber protein has been replaced with a heterologous fiber protein (claims 43, 46-51).

Romanczuk et al. teaches the production of chimeric adenovirus vector by modifying the capsid protein with a heterologous ligand to improve or alter the infectious capability of the vector. The vectors can be used to deliver a transgene into a cell (see abstract, claims 1, 2, 18 and 43). Although the specific examples provided in the reference utilize human adenovirus. The reference is not limited to a this particular adenovirus as any adenovirus falls within the

scope of the invention. The reference teaches how to make the particular modification as to alter the viral tropism. The reference does not specifically teach utilizing bovine adenovirus.

Reddy et al. teach the production of a replication defective bovine adenovirus (BAV-3) and a method of reducing occurrence of replication competent adenovirus by the use of a cell line that complements those deleted proteins. The complementing cell lines expresses the necessary components from human adenovirus sequences further reducing the likelihood of producing replication competent viruses in the system (see page 9143, column 1, 3rd paragraph). The reference expressly directs using BAV-3 as a viral vector for therapy in humans. For successful therapy, transfer vectors with very high transudation efficiency are needed. A strategy to achieve this is to replace the knob region of the fiber of BAV-3 with that of an HAV. This is possible, as the entry of ovine adenovirus into human cells was enhanced when the knob region of the fiber was replaced with that of HAV-5. The RGD motif, which interacts with surface integrins and facilitates the entry of virus into cells, is present in the penton base protein of HAV-5 but absent in BAV-3. Introduction of such a motif into BAV-3 may facilitate entry into human cells (see page 9143, last paragraph). The reference does not teach using bovine adenovirus vector type 1 or type 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a bovine adenovirus for the transuduction of human cell lines or for the use of the bovine adenovirus as a vaccine vector. Reddy et al. teaches producing a bovine adenovirus with altered tropism to infect human cells. Romanczuk et al. teaches a generic chimeric adenoviral vector to alter tropism. One having ordinary skill in the art would have been motivated to utilize a bovine adenovirus as a vaccine vector because the average human

population would not have produced neutralizing antibodies to bovine adenovirus as this virus would not normally infect the population. Utilizing a bovine adenovirus as a vaccine vector would also reduce the risk of recombination with wild type viral sequences creating a replication competent virus. Additionally utilizing BAV type 1 and 2 would allow for multiple vaccination with a bovine adenovirus vector as the subject would not have made neutralizing antibodies to the particular vectors. Therefore, the instant invention is obvious over Romanczuk et al. and Reddy et al.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 12/9/02